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Brief Communication

First COVID-19 mortality case in Taiwan with bacterial co-infection by national surveillance of critically ill patients with influenza-negative pneumonia

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Abstract A 63-year-old diabetic smoker with alcoholism was the first mortality case of coronavirus disease 2019 (COVID-19) in Taiwan. As concurrently infected with *Klebsiella pneumoniae* and subsequently with *Klebsiella aerogenes*, he was exposed by a national survey of patients with critically influenza-negative pneumonia. We recommend COVID-19 screening for patients with severe flu-like syndrome and protecting health-care workers from being infected.
**Klebsiella; Taiwan**

**Introduction**

Coronavirus disease 2019 (COVID-19) pandemic has infected more than 3 million people and caused above 200 thousand deaths by May 2020. We report the first COVID-19 mortality case of Taiwan, who was admitted due to severe community-acquired pneumonia (CAP), *Klebsiella pneumoniae* initially isolated. At the day of his death, via national surveillance of registered flu-like syndrome with severe complications, he was confirmed a victim of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and later co-infected with carbapenem-nonsusceptible *Klebsiella aerogenes* (CnSKA). The early detection and precaution of SARS-CoV-2-infected patients, especially in critical care units, are urgently needed for the safety measures of health-care workers and in-hospital patients.

**Case presentation**

A 63-year-old male gypsy cab driver with a history of diabetes mellitus, hypertension, and hepatitis B became ill with productive cough since January 25, 2020. Seven days later, he presented to a primary clinic with fever, myalgia, generalized malaise, and poor appetite. He smoked heavily and drank whiskey 300–500 ml daily for 20 years. According to his statement, neither he or his contact traveled abroad recently. No family members or contact had fever or symptoms of respiratory tract. Oseltamivir and azithromycin were prescribed for flu-like syndrome. Due to persisted fever and worsening dyspnea, he visited chest physician of this regional hospital two days later, then was admitted via emergency department (ED) because of hypoxemia.

The physical examination at ED revealed a body temperature of 38.3 °C, blood pressure of 119/85 mm Hg, pulse rate of 104 beats per minute, respiratory rate of 26 breaths per minute, and oxygen saturation level of 86% while breathing ambient air. Chest auscultation disclosed bilateral crackles and radiograph revealed diffuse reticular and alveolar pattern over bilateral lung fields (Fig. 1A). Arterial blood gas analysis at room air showed pH 7.43, PaCO$_2$ 24.8 mm Hg, HCO$_3^-$ 16.2 mmol/L, and PaO$_2$ 48 mm Hg, for which Venturi mask with oxygen flow of 15 L/min was employed. Electrocardiogram reveals sinus tachycardia. Laboratory results demonstrated a leukocyte count of 8450 per µL with a differential of 85% neutrophils, 10% lymphocytes, and 5% monocytes; a hemoglobin of 14.6 g/dL; platelets of 188,000 per µL. Elevations of serum creatinine (1.52 mg/dL), aspartate aminotransferase (96 U/L), creatinine kinase (496 U/L), and C reactive protein (CRP, 32.5 mg/dL) were noted. Under the impressions of severe CAP, suspecting influenza-like syndrome with secondary bacterial infection and acute respiratory distress, he was admitted to an airborne-isolation negative pressure room in intensive care unit (ICU) complying with infection control policy of this hospital. Initial antibiotic therapy consisted of peramivir 300 mg single injection, piperacillin 4 g/tazobactam 500 mg every 8 h, and vancomycin 1 g every 12 h

Although the throat swab for influenza was negative by a rapid test (SB Bioline, Abbott, South Korea) and a rapid nucleic acid amplification test (Alere, Abbott, USA), he was registered to Taiwan Centers for Disease Control (CDC) on admission day as a case of influenza infection with severe complications.

On the next day, his saturation down to 80% using non-rebreathing mask with 15 L/min oxygen flow, endotracheal intubation and mechanical ventilation were initiated. His condition fulfilled Berlin definition of acute respiratory distress syndrome (ARDS) and was managed with lung-protective ventilation strategy. His oxygen saturation was temporarily stabilized employing fentanyl, propofol, and cisatracurium pump for ventilator synchronization and norepinephrine for septic shock management. One dosage of 50 mg methylprednisolone was administered for treatment of wheezing dyspnea. Blood sugar was controlled with insulin injection subcutaneously.

Intermittent fever up to 39.8 °C persisted. Assays of serum *Mycoplasma pneumoniae* IgM, serum *Chlamydia pneumoniae* IgM, urine antigen of *Streptococcus pneumoniae*, acid-fast stain of sputum, serum antibody to hepatitis C virus, and serum antigen and antibody to human immunodeficiency virus test yielded negative results. Endotracheal aspirate demonstrated Gram-negative bacilli 2+ with phagocytosis on hospital Day 2, and later its culture grew wild type *K. pneumoniae* (WTKP; Supplement 1). Antibiotics was adjusted to 600 mg of ceftaroline and 200 mg of ciprofloxacin every 12 h.

On hospital Day 5, hypoxemia progressed though 95% FiO$_2$ use (Fig. 2). With the findings of neutrophil-predominant leukocytosis and enlargement of pneumonia patch, ventilator-associated pneumonia was suspected and colistin 4,000,000 U every 12 h was added empirically. Cefaroline was discontinued and teicoplanin administered. Carbapenem-nonsusceptible *K. aerogenes* (CnSKA) was cultured from endotracheal aspirates on hospital Day 12 and verified by next-generation sequencing (Supplement 1). Despite aggressive care, intermittent fever, hypoxemia and profound shock developed on the following days. Complying with family’s choice, Do-Not-Resuscitation was signed, and he died on hospital Day 13 (illness Day 22).

Without contact history, he was not qualified for the SARS-CoV-2 testing prior to February 15, when 113 nationally registered ICU patients with flu-like syndrome, influenza virus test-negative, were investigated for COVID-19 by Taiwan CDC. The oropharyngeal swab and later the biopsied lung specimen of this patient yielded a positive result for SARS-CoV-2, and at the day of his death, he was confirmed COVID-19 case NO. 19 of Taiwan. Taiwan CDC reported that this patient was infected on January 22 via contact with a SARS-CoV-2-infected businessman, who came back from Zhejiang, China, during a 30-min drive in his closed window cab. Four close relatives of this patient were tested...
positive for SARS-CoV-2, and among them, two were symptomatic and admitted to isolation room in hospital. All the 84 contacted health-care workers, who were isolated at home for 14 days, were tested negative for SARS-CoV-2. This patient was the first COVID-19 mortality case of Taiwan, also the 5th global mortality case outside China governance, and was the first case of proven viral-bacterial co-infection.

Figure 1. Chest Radiographs of Persistent Infiltrates and Gram-negative Bacilli Phagocytized by Neutrophils on Gram Stain of Endotracheal Aspirates during the hospital course, hospital Day 1 to Day 11. A. Posteroanterior chest radiograph, hospital Day 1. Diffuse reticular infiltrates in both lungs, indicating likely atypical pneumonia. A local alveolar infiltrate noted in right lower lung, arousing concern about the secondary bacterial infection. B. Anteroposterior (AP) chest radiograph, hospital Day 2. Note the progression of opacities in both lungs following intubation, fulfilling with acute respiratory distress syndrome accompanied with clinical condition and lab findings. C. AP chest radiograph, hospital Day 5. Worsening of bilateral infiltrates. Antibiotic regimen was adjusted to cover ventilator-associated pneumonia. D. AP radiograph, hospital Day 11. Persistent reticular infiltrates on both lungs and clinical condition still deteriorated. E. & F. Gram stain on hospital Day 12. Gram-negative bacilli were presented and phagocytized by neutrophils (arrow) under a high-power (1000×, oil immersion) objective.

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Discussion

For critically ill patients infected with SARS-CoV-2, the mortality rate can be as high as 61.5%. Here, we present a critically ill COVID-19 patient who infected with Klebsiella species concurrently and had concomitant leukocytosis and lymphopenia. The mortality of viral-bacterial co-infection is greater than that of either the viral or the bacterial infection alone. The condition of this patient met the criteria of severe CAP and needed the supports of ventilator and vasopressor. Although his lymphocyte count increased on illness Day 20, indicating the decline of SARS-CoV-2 viral loads, this patient still died of subsequent infections with CnSKA. In previous reports, the replication of influenza virus damaged the pulmonary epithelial cells which expose attachment sites for bacterial invasion and impairs bacterial clearance from the respiratory tract. The same is true for respiratory syncytial virus and adenovirus. S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus are common co-pathogens for viral pneumonia. Concurrent bacteremic pneumonia due to K. pneumoniae was reported in an influenza victim. The complication of secondary bacterial infections has been one of the major causes of influenza-associated death. The increased risk for secondary bacterial infections may be related to lymphopenia in more than 80% of reported COVID-19 patients. Directed T cell infection and depletion had been speculated in severe acute respiratory syndrome coronavirus 2; CRP, reactive protein; PaCO2, partial pressure of carbon dioxide; HCO3-, bicarbonate; PaO2, partial pressure of oxygen; SaO2, arterial saturation of oxygen; FiO2, fraction of inspiration oxygen. ARDS, acute respiratory distress syndrome; CXR, chest X-ray; CDC, Centers for Disease Control and Prevention.
invasive mechanical ventilation, and the old age and comorbidities, including hypertension, diabetes, and cardiovascular disease were predisposing factors. K. pneumoniae accounts for up to 17% of community-acquired pneumonia in Taiwan and 10–29% of ventilator-associated pneumonia in various countries. Klebsiella pneumonia generally presents with fulminant course and has poor prognosis. Initial acute respiratory failure and septic shock were independent risk factors for early mortality. It is vital to study and to treat secondary bacterial infections, including resistant strains, that likely complicate the disease with an increased mortality.

SARS-CoV-2 is very contagious and its transmission can occur when contacting with asymptomatic patients during their incubation period. This Taiwan Case NO. 19 driver was infected by a coughing businessman with serum SARS-CoV-2 antibody proved by Taiwan CDC. Three days after exposure in his cab, this No. 19 case developed flu-like symptoms for the next 7 days. He subsequently transmitted SARS-CoV-2 to four of his relatives at a family dinner. However, the healthcare workers were not infected by strict compliance with hospital infection prevention and control rule. Since the contacts were all isolated for 14 days, there was no further outbreak. It is urgent that SARS-CoV-2 should be screened for flu patients with severe illness.

In conclusion, for hospitalized patients with flu-like symptoms in endemic area, common respiratory pathogens, such as influenza and SARS-CoV-2, should be investigated. Multiplex PCR pneumonia panels may be applied for detection of common respiratory bacterial pathogens and resistance determinants. Empirical anti-bacterial antibiotics should be based on local epidemiologic data, especially for the elderly and patients with high risk of mortality. Moreover, hospital-acquired pneumonia should be alerted if the clinical condition is deteriorating. For those unidentified yet high risk contacts, quarantine should be launched to protect healthcare workers from acquiring COVID-19.

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Appendix

Supplement 1. Antimicrobial susceptibility test of K. pneumoniae isolate on hospital Day 2 and Klebsiella aerogenes isolate on Day 12.  

| Isolate | Hospital Day | K. pneumoniae | Klebsiella aerogenes |
|---------|--------------|---------------|---------------------|
|         | Day 2        | MIC (µg/ml)a  | MIC (µg/ml)a        |
|         |              | R  >16       | R  >16              |
| Ampicillin |              | S  ≤10     | S  ≤8                |
| Amikacin  |              | S  ≤8       | S  ≤8                |
| Ceftazidime |            | S  ≤10     | S  ≤10               |
| Ceftriaxone |             | S  ≤10     | S  ≤10               |
| Cefotaxim |              | S  ≤10     | S  ≤10               |
| Ertapenem |              | S  ≤0.25   | S  ≤0.25             |
| Ceftipime |              | S  ≤0.25   | S  ≤0.25             |
| Gentamicin |              | R  >16     | R  >16               |
| Imipenem  |              | S  ≤0.25   | S  ≤0.25             |
| Levofloxacin |            | R  >4      | R  >4                |
| Meropenem |              | S  ≤0.25   | S  ≤0.25             |
| Ampicillin/Sublactam | | S  ≤4/2 | R  >16/8             |
| Tigecycline |            | S  1       | I  4                 |
| Piperacillin/Tazobactam | | S  ≤4/4 | I  64/4             |

a Antimicrobial susceptibility testing was performed with standard broth micro-dilution method and interpreted based on the criteria from the Clinical and Laboratory Standards Institute guidelines (M100-ED29; Table 2A).